REMARKS/ARGUMENTS

In the Office Action mailed May 18, 2009, the amendment and response filed on 27 March 2009 was considered non-compliant due to an incorrect status identifier for claim 21. Applicants submit that the change in claim 21 from "31 and" to "31, and" was due to a clerical error. The erroneous comma has been removed herein. Accordingly, the correct status identifier of "(Previously Presented)" has been retained.

In the Office Action mailed September 29, 2008 (Hereinafter referred to as, "the Office Action"), claims 19-39 and 41-43 were rejected and claim 40 was found allowable. Applicants have thoroughly reviewed the outstanding Office Action including the Examiner's remarks and the references cited therein. The following remarks are believed to be fully responsive to the Office Action.

Initially, Applicants wish to thank the Examiner for allowing claim 40. Without conceding to the propriety of the rejections under 35 U.S.C. §112, Applicants respectfully submit that all remaining claims have been amended to include subject indicated as allowable and are therefore also in condition for allowance. No new matter has been added by these amendments and no estoppels are intended thereby. Claim 22 has been amended to recite the antibody comprises the dominant sequence and is therapeutically effective against *Clostridium difficile*. Support for this amendment is found throughout the specification, for example, on page 1, lines 3-5. Claim 41 has been amended in a manner similar to claim 40 which has been found allowable. Claims 42 and 43 have been amended to recite an additional step (iv) which corresponds to step (iii) of claim 1 (previously cancelled).

DOUBLE PATENTING

Claims 19, 20, and 21 have been provisionally rejected on the grounds of nonstatutory obvious-type double patenting as being unpatentable over claims 22-36 of copending Application No. 11/630,926. Without conceding the propriety of the provisional double patenting rejection, a terminal disclaimer in compliance with 37 CFR 1.321(c) will be filed to obviate the double patenting rejection at such time this is the sole remaining rejection.

CLAIM OBJECTIONS

Claim 41 stands objected to because of an informality. Specifically, a penultimate "and" was inadvertently omitted between steps (i) and (ii). Claim 41 has been amended to include the penultimate "and".

CLAIM REJECTIONS – 35 U.S.C. §112

Claim 41 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states:

> The claim is drawn to a method for identifying candidate antigen-specific sequences of antibodies specific against at least one antigen produced by *C. difficile* comprising: (i) obtaining B cells from two or more patients whose immune systems have been exposed to the antigen and sequencing from the B-cells of both patients at least CDR3 regions of VH or VL, or both; and, (ii) detecting a set of sequences that occur in the two or more patients in total at a frequency of at least one percent wherein the set of sequences include a dominant sequence and sequences of at least 80% homology to the dominant sequence, and wherein the detection of the set of sequences in the two or more patients confirms that the set of sequences is specific against *C. difficile.*
>
> While the claim may determine sequences that occur in two or more patients in total at a frequency of at least one percent, it is unclear how one determines that the antibodies are "specific against at least one antigen" of *C. difficile.* In step (i), one collects all B-cells, not just B-cells which may interact with a *C. difficile* antigen. Thus, the B-cell population is a heterologous population, containing cells reactive to any number of unknown moieties. In step (ii), the only criterion for selection is a frequency of $\geq$1% for CDR3 regions of VH or VL or both. There is no restriction to the reactivity of the regions. Thus, if both of the patients were currently

> in an active B-cell immune response to another moiety, these CDR3 regions would probably meet the only criterion for selection. This permits selection of non-*C. difficile* antibodies. Therefore, the claim is unclear how one distinguishes between *C. difficile* antibodies and antibodies against any other moiety.

Applicants respectfully submit that the amendment to claim 41 renders the foregoing rejection moot. Claim 41 has been amended in a manner similar to allowed claim 40 to recite a step of confirming that an antibody or an antigen binding fragment of an antibody comprising the dominant sequence of step (ii) binds specifically to the antigen produced by *Clostridium difficile*. Accordingly, Applicants believe this rejection has been overcome and earnestly solicit the withdrawal of this rejection.

Claim 42 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states:

> The claim is drawn to a method for identifying candidate antigen-specific sequences of antibodies specific against at least one antigen produced by *C. difficile* comprising: (i) obtaining B cells from at least one patient whose immune system has been exposed to the antigen and sequencing from the B-cells at least CDR3 regions of VH or VL, or both, (ii) comparing the sequences of step (i) with sequences of at least CDR3 regions of VH or VL, or both, from a patient that has not been exposed to the antigen, and (iii) detecting a set of sequences that occur in total at a frequency of at least one percent in the sequences identified in step (i) and at a frequency of less than one percent in the sequences from the non-exposed patient, wherein the set of sequences include a dominant sequence and sequences of at least 80% homology to the dominant sequence.
>
> While the claim does determine sequences that occur in total at a frequency of at least one percent of the exposed patient, but at a frequency of less than one percent in the sequences from the non-exposed patient, it is unclear how one determines that the antibodies are "specific against at least one antigen" of *C. difficile*. In step (i), one collects all B-cells, not just B-cells which may interact with a *C. difficile* antigen. Thus, the B-cell population is a heterologous population, containing cells reactive to any number of unknown moieties. In step (ii), the only criterion for selection is a frequency of $\geq$1% for CDR3 regions of VH or VL or both in an exposed patient, while the only criterion for selection is a frequency of $\leq$1% for CDR3 regions of VH or VL or both in a non-exposed patient. There is no restriction to the reactivity of the regions. If the exposed patient was currently in an active B-cell immune response to any other moiety, these CDR3 regions would probably meet the only criterion for selection. Therefore, the claim is unclear how one distinguishes between *C. difficile* antibodies and antibodies against any other moiety.

Applicants respectfully submit that the amendment to claim 42 renders the foregoing rejection moot. Claim 42 has been amended to recite a step of confirming that an antibody or an antigen binding fragment of antibody comprising the dominant sequence of step (iii) binds specifically to the antigen produced by *Clostridium difficile*. Accordingly, Applicants believe this rejection has been overcome and earnestly solicit the withdrawal of this rejection.

Claim 43 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states:

> The claim is drawn to a method for identifying candidate antigen-specific sequences of antibodies specific against at least one antigen produced by *C. difficile* comprising: (i) obtaining B cells from at least one patient prior to exposure of their immune system to the antigen and sequencing from the B-cells at least CDR3 regions of VH or VL, or both, (ii) obtaining B cells from said patient after exposure to the antigen and sequencing from the B-cells at least CDR3 regions of VH or VL, or both; and (iii) detecting a set of sequences that occur in total at a frequency of at least one percent in the sequences identified in step (ii) and at an increased frequency with respect to the sequences identified in step (i), wherein the set of sequences include a dominant sequence and sequences of at least 80% homology to the dominant sequence.
>
> While the claim may determine sequences that occur in total at a frequency of at least one percent in the patient following exposure to the antigen, it is unclear how one determines that the antibodies are "specific against at least one antigen" of *C. difficile*. In both step (i) and step (ii), one collects all B-cells, not just B-cells which may interact with a *C. difficile* antigen. Thus, the B-cell population is a heterologous population, containing cells reactive to any number of unknown moieties. In step (iii), the only criterion for selection is a frequency of $\geq$1% in the sequences identified in step (ii) and at an increased frequency with respect to the sequences identified in step (i). There is no restriction to the reactivity of the regions. If the patient was simultaneously exposed to any other moiety at the time of exposure to said *C. difficile* antigen, these CDR3 regions would probably meet the only criterion for selection. Therefore, the claim is unclear how one distinguishes between *C. difficile* antibodies and antibodies against any other moiety.

Applicants respectfully submit that the amendment to claim 43 renders the foregoing rejection moot. Claim 43 has been amended to recite a step of confirming that an antibody or an antigen binding fragment of an antibody comprising the dominant sequence of step (iii) binds specifically to the antigen produced by *Clostridium difficile*. Accordingly, Applicants believe this rejection has been overcome and earnestly solicit the withdrawal of this rejection.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request that all the objections and rejections to the claims be removed and that the claims pass to allowance. If, for any reason, the Examiner disagrees, please call the undersigned at 202-861-1629 in an effort to resolve any matter still outstanding before issuing another action. The undersigned is confident that any issue which might remain can readily be worked out by telephone.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiencies or credit any overpayments to Deposit Account No. 50-2036 with reference to our Docket No. 87278.2760.

Respectfully submitted,
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